UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,301	01/08/2001	Junming Le	0975.1005-008	5453

21005 7590 09/29/2003

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/29/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/756,301	LE ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2,4-19,21-33,37,40-42,45 and 48-55* is/are pending in the application.

4a) Of the above claim(s) *16 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) *17,37,40-42,45 and 48-55* is/are allowed.

6)☐ Claim(s) *1,2,4-15,18,19 and 21-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10, 10/2
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 3, 20, 34-36, 38, 39, 43, 44, 46 and 47 have been canceled. Claims 16 and 33 remain withdrawn from consideration. Claims 1, 2, 4-15, 17-19, 21-32, 37, 40-42, 45 and 48-55 are under consideration..

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. The objection to the disclosure and the Oath or Declaration for reciting priority to application 09/133,119 as a divisional application is withdrawn.

4. The objections to the specification for not complying with 1.821(d) of the Sequence Rules and Regulations as set forth in Papers 9 and 14 are withdrawn in light of applicants amendments and arguments.

5. The terminal disclaimer filed on January 23, 2003 has been reviewed and is accepted. The terminal disclaimer has been recorded.

6. The rejection of claims 1, 2, 4-15, 18, 19, 21-32 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record.

Claims 1 and 18 are rendered vague and indefinite in the recitation of epitope specific for human TNF alpha. It is unclear if the specificity is to be evaluated in relation to TNF alpha of other species such as rabbit or mouse, or if the specificity is to be evaluated in relation to human TNF-beta or gamma.

Applicant argues that the instant specification clearly teaches that the claimed antibodies are specific for human TNF alpha when evaluated in relation to TNF alpha of other species and when evaluated in relation of human TNF-beta or gamma and cites the instant specification at page 81, line 13 to page 83 line 10 for support. This has been

considered but not found persuasive. The cited text describes the reactivity of the cA2 antibody. The specification does not contemplate a larger genus of antibodies having the identical specificity of the cA2 antibody. Further, the cA2 antibody was found to bind to chimpanzee TNF alpha and it is stated on page 82 that "the epitope recognized by A2 is one shared by human and chimpanzee TNF alpha". Therefore antibodies which specifically bind to human TNF alpha cannot be construed to mean antibodies that only bind to human TNFalpha. Further, this statement does not place a limitation on the specificity of the genus of antibodies claimed and further raises questions as to the meaning of the term "specific" when used in the context of describing the binding of the claimed antibodies. If binding to chimpanzee TNFalpha is within the tolerance of what the applicant regards as specifically binding human TNF alpha, then it would be reasonable to conclude that other antibodies which bind to human TNF alpha and, for instance, the TNFalpha of the rhesus monkey could also be classified as specific for human TNF alpha. Amendment of the claim to incorporate the A2 epitope would overcome this rejection as the species specificity would be inherent with the presence of the epitope.

Claims 7 and 24 recite "high affinity". The term "high affinity" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree. Therefore, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Recitation of Ka values that are preferred embodiments, such as those given in the specification on page 61, lines 3-5, does not constitute a definition of what applicant considered "high affinity".

Applicant argues that the term "high affinity" is a standard term used in the art to describe and antibodies affinity for its ligand. Applicant refers to the publication of Moller et al who describes "high affinity monoclonal antibodies" in a Table, and that one would understand based on an antibodies binding affinity for its ligand whether the antibody bound with low, moderate or high affinity. This has been considered but not found persuasive. The MPEP (2171) states that there are two requirements necessary to satisfy under 35 U.S.C. 112, second paragraph. The first is that the claims must set forth the subject matter that applicants regard as their invention; and the second is that the

claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.

Claims drawn to "high affinity" lack a specific definition in the specification and therefore do not meet the requirements of 112, second paragraph because they do not ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. Based on the instant specification, it would not be possible to determine the border between "high affinity" antibodies and antibodies which are not high affinity antibodies. Applicant argues that the term "high affinity" is a standard term in the art. This is not persuasive. Although the art recognizes the meaning of antibody affinity, there is no definition in the art which would dictate the border between high affinity antibodies and non-high affinity antibodies. The term "high affinity" is although used frequently is determined by the particular laboratory, and thus the term is routineer specific.

The rejection of claim 17 for the recitation of "cA2" as the sole means of identifying the claimed antibody is withdrawn . Applicant argues that the antibody cA2 is well known in the art as evidenced by two scientific publication regarding the administration of the antibody to humans, and that further, the antibody has been disclosed in prior patents. This has been considered and found persuasive. The instant and prior patents have disclosed the cA2 antibody as consisting of the light and heavy chain variable regions of SEQ ID NO:3 and SEQ ID NO:5, respectively, fused to the constant region of human IgG1 kappa .

7. The rejection of claims 11-13 and 28-30 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained reasons of record.
Claims 11 and 28 are drawn to antibodies and polypeptides having a ID50 of at least 1 ug/ml, 15 ng/ml and 100 ng/ml, respectively. The specification teaches on page 53, lines 25-26 that cA2 has an ID 50 of 17 mg/ml as determined by an in vitro cytotoxicity assay. The specification sets forth on page 72 and figure 3 the results of an in vitro cytotoxicity

assay with the cA2 antibody. It is noted that in figure 3 the concentration of the antibody is given in ng/ml. Claims 11-13, 28-30 and 52-54 are drawn to ID50s on the order of ug/ml and ng/ml. Given the inconsistencies within the specification, one of skill in the art would not know how to make or use the claimed antibodies having the recited ID50 values, because one of skill in the art would not be able to ascertain the actual ID50 of the cA2 antibody. Therefore, one of skill in the art would be subject to undue experimentation in order to make and use the claimed antibodies having specific ID50 values.

Applicant argues that there are no inconsistencies within the specification as Figure 3 indicates a 1000 ng/ml concentration point which is equal to 1 microgram/microliter and that it is within the purview of one of skill in the art to convert nanograms per ml to micrograms per ml. This has been considered but not found persuasive. The issue is not the ability of one of skill in the art to convert the units representing concentration, but the conflicting teachings of the specification on page 53, lines 25-26 which state that the cA2 antibody has an ID 50 of 17mg/ml which is in direct conflict with the teachings of Figure 3 as stated in the grounds of rejection. It is noted that the teachings of the concentrations on page 53 differs from the teachings of the concentrations in Figure 3 by an order of magnitude.. The rejection is withdrawn on claims 52-54 because the binding affinities would be inherent in the variable chains of SEQ ID NO:3 and SEQ ID NO:5.

8. The rejection of claims 1, 2, 4-10, 14, 15, 18-27, 31, 32 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for chimeric antibodies containing all of the variable regions of the parent non-human antibody, said chimeric antibody having unspecified binding affinity for TNF alpha does not reasonably provide enablement for antibodies or polypeptides which compete with cA2 for binding to hTNF, chimeric antibodies which are not cA2 having Ka values of at least 1 X 10^8 L/mole or 1 X 10^9 L/mole, or fragments of antibodies or polypeptides, thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 9 and 10, 26 and 27 are drawn to chimeric antibodies comprising part of a human immunoglobulin constant domain and part of a non-human variable region said antibodies binding to TNF alpha with the affinity constants of 1×10^8 or 1×10^9. Claims 8 and 25 are drawn to chimeric antibodies which competitively inhibit the binding of cA2 to TNF alpha. The specification teaches on page 81 lines 5-7 that it was an unexpected that the chimeric A2 antibody, termed the cA2 antibody, had an affinity constant that was higher than the parent murine antibody as it would be expected that a chimeric antibody would have an affinity constant that was equal to or lower than that of the parent antibody. The specification teaches that the cA2 antibody consists of both heavy and light chains of the murine A2 antibody, in addition to the human constant regions of Ig gamma 1 and kappa. The specification provides no special teachings for how to make other chimeric anti-TNF antibodies that would duplicate the claimed high affinity constants. Further, the art teaches that chimeric and humanized antibodies often have decreased binding affinity relative to their murine counterparts (Mateo et al, Hybridoma, 2000, Vol. 19, pp. 463-471). Adair et al (WO 92/11383, reference AL4 of the IDS filed July 3, 2001) teach how to make a chimeric humanized antibody to TNF alpha, said humanized antibody comprising a human framework in which murine CDR sequences have been inserted. Adair et al point out that in order to obtain a humanized antibody having satisfactory binding affinity, it is necessary to alter certain amino acids within the framework of the variable region (page 6, last bridging paragraph). Thus, given the teachings of the specification regarding the unexpected high binding affinity of the cA2 antibody, the teachings of the recent art regarding the expectation of lower binding affinity for a chimeric antibody, and the teachings of Adair et al regarding the necessity of altering framework regions to improve binding affinity, it can be concluded that the specification is lacking in teachings on how to make other chimeric antibodies which bind to TNF alpha with the claimed affinity constants or having the ability to competitively inhibit the binding of cA2 to TNF alpha, as said inhibitor would need to possess an affinity constant of a similar order of magnitude as cA2 in order to compete

with cA2 in binding to TNF alpha. Given these lack of teachings and the unpredictability of the art as exemplified by Mateo et al and Adair et al, a person of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make chimeric antibodies other than cA2 which would have the claimed affinity constants.

Claims 1, 2, 4-10, 14, 15, 18, 19, 21-27, 31 and 32 encompass chimeric antibodies containing less than all of the light and heavy chain variable regions of a parent non-human antibody. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. Paul (Fundamental Immunology, (text), 1993, pages 292-293) teaches that the structure of the variable chain provides the three dimensional context in which different amino acids interact to form ligand binding sites. Paul further teaches that the CDR regions contained in the variable chain are brought together by dimerization of the heavy and light chain variable regions (page 293, first column lines 3-8) to form the ligand binding surface and that sequence variation within the CDR alters ligand recognition. Thus it cannot be expected that antibodies or polypeptide comprising less than the full variable regions of the parent antibody will form an identical ligand binding surface. Further the result of altering the sequence context around the CDR cannot be anticipated as the relative positions and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. Paul further teaches that CDR loops can interact with framework regions as evidenced by work with humanized antibodies (page 293, second column, lines 9-12). It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation are required in order to produce a protein having antigen-binding function. Thus the proper association and sequence context of the heavy and light chain variable regions is required in order to form functional antigen binding sites. It is unlikely that antibodies, polypeptides or fusion proteins as defined by the claims which contain less

than the full heavy and light chain variable regions of the cA2 antibody and fused to any human framework sequence or comprised by any polypeptide sequence would have the required binding function. The specification provides no direction or guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional humanized antibody can be obtained by replacing the CDR regions of an acceptor human antibody with the CDRs of murine anti-TNF alpha antibody. As evidenced by Adair et al. (WO 92/11383) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (page. 4, last paragraph). Adair et al demonstrates that amino acid residues in the framework region are involved in antigen binding by a humanized anti-TNF alpha antibody (page 6, last paragraph to page 7, line 4). Thus, there is no support in the specification for a nexus between the properties of the cA2 antibody to any or all of the myriad antibodies and polypeptides which are encompassed within this language. . One of skill in the art would neither expect nor predict the appropriate functioning of the antibodies or polypeptides as broadly as is claimed. Therefore, in view of the lack of guidance in the specification and in view of the discussion above, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to chimeric antibodies containing a portion of the variable region of a parent antibody.

Applicant argues that the court decision in In re Wands, provided in exhibit D, indicates that some experimentation, such as routine screening would not be undue experimentation in the monoclonal antibody art . Applicant points to other patents which have issued, such as US 6,284,471, which are drawn to chimeric antibodies comprising a portion of cA2. This has been considered and found partially persuasive. It is noted that in the issued patents, the claims are limited by structure to portions of SEQ ID NO:3 and SEQ ID NO:5 which are the variable heavy and light chains of cA2. Thus, one of skill in the art would not be subject to undue experimentation to be able to make the antibodies of claims limited by polypeptide sequence. Accordingly the rejection has been

withdrawn on claims 37, 40-42, 45 and 48-51. The rejection is maintained on claims not limited by polypeptide structure. As stated in the rejection above, it was an unexpected result the cA2 antibody had a higher binding affinity for TNF then the parent A2 antibody. This is corroborated by the teachings of Mateo et al (ibid) who teach that a loss of binding affinity relative to the murine parent antibody is commonly observed. Claims not limited by polypeptide structure are not limited to antibodies which are structurally related to the cA2 antibody and the claims are not limited to antibodies which bind the A2 epitope. Given this breath of the claims, it would be undue experimentation without reasonable expectation of success in order to make chimeric antibodies which bind to TNF with affinity constants of 1×10^8 or 1×10^9, or which can inhibit the binding of cA2 to TNF alpha.

Applicant argues that the specification fully enables the practice of the claimed invention because the starting material for making the claimed antibodies are well known in the art and that the specification teaches a method for cloning an anti-TNF variable region. Applicant argues that it would be easy to screen the chimeric antibodies to find those that compete with cA2 for binding to TNF. This has been considered but not found persuasive. The specification teaches a method of an anti-TNF variable region from A2. It would be necessary to have the non-human antibody in hand before the cloning, and given the teachings of the specification regarding the unexpected properties of chimeric A2 versus murine A2, one of skill in the art could not anticipate which parent antibody would give them a chimeric antibody which bound to TNF with a affinity similar to cA2. The specification does not teach the properties of A2 which were responsible for the unexpected result. Therefore one of skill in the art, given a panel of anti-TNF murine antibodies, which antibody would have the desired properties.

Applicant argues that the scope of the claims is commensurate with the scope of the enablement set forth and as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims then the enablement requirement is satisfied. This has been considered but not found persuasive. Applicant has provided the structure and function

of cA2. This is clearly not commensurate in scope with the instant claims which are not limited by structural relationship to cA2 or by binding the same epitope as cA2.

9. The rejection of claims 1, 2, 4-7, 15, 18, 19, 21-24 and 32 under 35 U.S.C. 103(a) as being unpatentable over Moller et al (Cytokine, 1990, Vol. 2, pp. 162-169, reference AX4 of the IDS filed July 9, 2001) in view of Zerler (EP 380,068, reference AP of the IDS filed July 9, 2001) as evidenced by Morrison et al (In: Antibody Engineering, (monograph) 1995, Ed. Borrebaeck, page 291) is maintained for reasons of record.

Claim 1 is drawn to a chimeric antibody comprising at least a part of a human immunoglobulin constant region and at least a part of a non-human variable region, said antibody capable of binding an epitope specific for human tumor necrosis factor alpha. Claim 18 is drawn to the chimeric antibody of claim 1 with the added embodiment of IgG1 as the human constant region. Claims 2 and 19 specifically embody the antibodies of claims 1 and 18, respectively, wherein the binding of said antibodies to TNF alpha inhibits a pathological activity of TNF alpha. Claims 4 and 21 specifically embody the antibodies of claims 1 and 18, respectively, wherein said chimeric antibody two light and two heavy chains comprising at least a part of a constant region and a part of a variable region. Claims 5 and 22 specifically embody the chimeric antibodies of claims 1 and 18, respectively, wherein said antibody neutralizes TNF alpha under physiological conditions. Claims 6 and 23 further embody a variable region of murine origin for the antibodies of claims 1 and 18, respectively. Claims 7 and 24 further specify that the antibodies of claims 1 and 18 are derived from a high affinity murine monoclonal antibody which binds to a neutralizing epitope of TNF alpha. Claims 14 and 31 specifically embody the antibodies of claims 1 and 18 in detectably labeled form; claims 15 and 32 specifically embody the chimeric antibodies of claims 1 and 18 which are produced recombinantly.

Moller et al teach the murine mAb 195 (page 163, first column under "Production of Monoclonal Antibodies") which specifically binds to an epitope of TNF alpha that is present on human TNF alpha and Chimpanzee TNF alpha and does not show any cross-reactivity with other human proteins including TNF-beta (page 164, second column under

the heading "Characterization of Monoclonal antibodies by Immunoblot" and page 165 first column, lines 3-5). Moller et al teach that mAb 195 neutralized the cytotoxic activity of human TNF alpha in vitro (page 164, first column and Table 2, second column). Moller et al also teach that administration of the mAb 195 to mice injected with human TNF alpha blocked the lethal effect of TNF in the mice (page 165, second column, under the heading "Neutralization of Human TNF Alpha in the Mouse). Additionally the mAb 195 was detectably labeled with biotin (page 167, first column under the heading of "Biotinylation of Monoclonal Antibodies") thus fulfilling the embodiments of claims 14 and 31. Thus, Moller et al teach a murine antibody which specifically binds to an epitope of human TNF alpha, wherein said antibody is a high affinity murine monoclonal antibody (defined as by the ability to block the activity of THF alpha in vitro as stated in the rejection under 35 U.S.C. 112, 2nd paragraph, section 6, above), and the inhibition of a pathological activity of TNF alpha (TNF-induced lethality), the neutralization of TNF alpha under physiological conditions (within the mouse). Moller et al do not teach a chimeric antibody comprising part of a human constant region, nor a human IgG1 constant region.

Zerler et al teach a chimeric antibody comprising part of a human constant region derived from murine antibodies which bind to the Il-2 receptor. Zerler et al teach a general method for how to make recombinant chimeric antibodies comprising a IgG1 human constant regions (page 5, lines 53-55) and murine variable regions. Zerler et al suggest that chimeric antibodies against TNF can be made in a similar method (page 10, line 55 to page 11, line 8). Zerler et al teach the expression of the vector encoding the chimeric antibodies in mammalian cell lines transformed by said vector (claim 13). Zerler et al do not specifically teach that the recombinant chimeric antibody obtained from the disclosed method would contain two light chains and two heavy chains. Morrison et al teach (page 291, under the heading "Things to Consider") that transfectomas generally secrete IgGs as H2L2 (two heavy chains and two light chains). Thus, it would be reasonable to assume that the transformed mammalian cells taught by Zerler et al secrete chimeric antibodies having two light chains and two heavy chains.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a chimeric antibody having a IgG1 constant region, wherein the variable region was derived from mAb195. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Zerler et al regarding the advantages of chimeric antibodies versus murine antibodies such as the elimination of allergic side effects and the increase in serum half live (page 3, lines 29-33), and the suggestion of Zerler et al, that the disclosed methods of making the recombinant chimeric antibodies could be applied to antibodies against TNF. Zerler et al specifically teach that an antibody having a human IgG1 constant region has a serum half-life of 21-23 whereas a murine antibody has a serum half life of 15-16 hours.

Applicant argues that the antibodies of Moller et al are not chimeric but mouse monoclonal antibodies. Applicant points out that Moller fails to report a HAMA response or suggest the use of a chimerized antibody for human treatment, or suggest that the HAMA response could be significantly reduced by chimerization. This has been considered but not found persuasive, as the motivation to chimerize the anti-TNF antibody taught by Moller et al is supported by the Zerler et al reference. Applicant further argues that Moller et al fail to describe antibodies which possess the characteristics of the claimed chimeric antibodies and points out that the mAB114 antibody taught by Moller et al shows cross reactivity to cynomolgus, rhesus and baboon TNF alpha. However, this argument is irrelevant as Moller et al was used in the rejection as teaching the mAb 195 antibody, not the mAb114, wherein the mAb195 antibody has the same binding specificity as the instant cA2 antibody in that it binds human and chimpanzee TNFalpha and does not bind TNFalpha from species which cA2 itself does not bind, as indicated in Table 2. Applicant argues that Moller et al does not report on the in vivo neutralizing ability of the antibodies and that the in vitro studies taught in Moller et al were limited to determining the ability of the antibodies to bind to TNF and to alter some of its biological activity, and that these in vitro studies do not suggest the clinical protocol or results of effective administration of anti-TNF antibodies in humans. This has been considered but not found persuasive. Moller et al conducted in vivo studies in mice wherein administration of the mAb195 antibody blocked the lethal effect

of human TNFalpha injected into the mice . It is noted that claims 2 and 19 carry the specific embodiment of the antibody inhibiting the pathologic activity of TNF, which would be met by the disclosure of Moller et because lethality would be a pathologic activity. Claims 5 and 22 carry the specific embodiment of neutralizing human TNF under physiological conditions. The teachings of Moller et al would meet the limitations of neutralizing human TNG alpha under physiological conditions as the antibodies were able to block the lethality of human TNF in a mouse, which constitutes physiological conditions. Applicant argues that Moller et al do not establish that anti-TNF antibody administration would have any effect on TNF-mediated disease in vivo, or the magnitude and duration of the clinical response and possible adverse reaction of that therapy. This is not persuasive. One of skill in the art would recognize that an antibody to TNFalpha would be effective in the treatment of TNF-mediated diseases, as it was well known that TNF is a mediator of toxic shock. This would be known to Moller et al at the time of his publication. Further, it would be obvious that the treatment of human TNF-mediated diseases would be part of the motivation of Moller et al to test the ability of the mA195 antibody to bock the lethal effect of human TNF in vivo. If the only motivation for obtaining an anti-human TNFalpha antibody were as a diagnostic test for the presence of TNFalpha, Moller et al would not have done the in vivo experiment because laboratory experiments with mice are costly and time consuming. Clearly, one of skill in the art on reading Moller et al would recognize the experiment in mice to be a pre-clinical experiment. Applicant states that because TNFalpha is known to have many epitopes, a skilled artisan, on the basis of the information disclosed in the reference[s] would not conclude that any of the prior art antibodies are identical or contain features of the antibodies claimed by the applicants. This has been considered but not found persuasive. Based on the teachings of Moller et al it would be concluded that there were no evidence to suggest that the mAb195 did not bind the same epitope of human TNFalpha as the instant cA2 as Table 2 in Moller et al indicates that mAb195 has the identical species specificity as reported for the cA2 antibody on page 81, line 28 to page 4.

Applicant argues that Zerler et al does not provide the teachings lacking in Moller et al because Zerler et al teaches only a generic expression system for producing chimeric

antibodies that allows for the insertion of non-human variable regions. This has been considered but not found persuasive. Zerler et al suggest that chimeric antibodies against TNF can be made in a similar method (abstract and page 10, line 55 to page 11, line 8). Zerler et al points out the motivation for making a chimeric antibody is to reduce the immunogenicity of the antibody in the human immune system and to increase the serum half-life of the antibody (page 3, lines 29-33). The examiner contends that this is adequate motivation for making the chimeric antibody from the mAb195 antibody disclosed by Moller et al.

10. The rejection of claims 1, 2-7, 15, 18, 19, 21-24, 32 under 35 U.S.C. 103(a) as being unpatentable over Moller et al (Cytokine, 1990, Vol. 2, pp. 162-169) and Zerler (EP 380,068) and Morrison et al (In: Antibody Engineering, (monograph) 1995, Ed. Borrebaeck, page 291) as applied to claims 1, 2, 4-7, 15, 18, 19, 21-24 and 32 above, and further in view of Socher et al (PNAS, 1987, Vol. 84, pp. 8829-8833) as evidenced by the abstract of Goh (Annals of the Academy of Medicine, 1990, Vol. 19, pp. 235-239) is withdrawn in light of applicants cancellation of claims 3 and 20.

11. The rejection of claims 34-36, 38, 39, 46 and 47 under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 3 and 5-9 of prior U.S. Patent No. 6,284,471 is withdrawn in light of the cancellation of claims 34-36, 38, 39, 43, 44, 46 and 47.

12. The rejection of claims 1, 4, 15, 18, 21, 32 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 5-7 of U.S. Patent No. 6,284,471 is withdrawn in light of applicants terminal disclaimer filed on January 23, 2003..

13. The rejection of claims 1, 4, 6, 8, 15, 18, 21, 23, 25, 32, 37, 40, 48, 49 and 55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 and 38 of copending Application No. 09/756,161 is withdrawn in light of abandonment of the '161 application.

The rejection of claims 17, 37, 40-42, 45 and 50-55 under the judicially created doctrine of double patenting over claims 1, 3 and 5-9 of U. S. Patent No 6,284,471 is withdrawn in light of the terminal disclaimer filed on January 23, 2003.

14. All other rejections and objections as set forth in Paper no. 9 are withdrawn.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
9/22/03